FILE 'CAPLUS, MEDLINE, BIOSIS, CA, SCISEARCH, EMBASE' ENTERED AT 12:28:17 ON 27 NOV 2002

L1 101944 S LIPOSOME OR IMMUNOLIPOSOME
L2 119313 S COMPLEX (S) FREE
L3 634 S L1 AND L2
L4 268 DUPLICATE REM L3 (366 DUPLICATES REMOVED)
L5 3774411 S ANTIBOD? OR LIGAND#
L6 28 S L4 AND L5

L8 ANSWER 1 OF 12 SCISEARCH COPYRIGHT 2002 ISI (R)
TI Efficient intracellular delivery of 5-fluorodeoxyuridine into colon cancer cells by targeted immunoliposomes
AB Immunoliposomes, liposomes with **monoclonal** antibodies attached, are being developed for targeting the anti-cancer drug 5-fluoro-2'-deoxyuridine (FUdR) to colon cancer cells. A **monoclonal** antibody against the rat colon carcinoma CC531 was covalently coupled to liposomes containing a dipalmitoylated derivative of the anti-cancer drug FUdR (FUdR-dP) as a prodrug in their bilayers. We studied the association with the **tumor** cells of different types of immunoliposomes varying in the position and orientation of the antibody at the **liposome** surface. We also assessed the in vitro anti-**tumor** activity of these liposomes and the mechanism by which the active drug FUdR is delivered intracellularly. Specific binding of the immunoliposomes to the **tumor** cells was observed. Immunoliposomes containing FUdR-dP caused a much stronger inhibition of CC531 cell growth in vitro than FUdR-dP in non-targeted liposomes. After binding to the cell surface only limited amounts of the immunoliposomes were internalized. By contrast, already within 24 h **immunoliposome**-incorporated FUdR-dP was hydrolyzed virtually completely to the parent drug FUdR, intracellularly. The mechanism of intracellular delivery of the drug most likely involves a selective transfer of the lipophilic prodrug from the liposomes to the cell membrane and subsequent intracellular processing. In conclusion, we developed a targeted liposomal formulation, which is able to deliver FUdR to colon carcinoma cells intracellularly with high efficiency, without the need for the cells to internalize the liposomes as such. This approach may be attractive for other lipophilic anti-cancer (pro)drugs. In this sense our system also serves as a model for the development of new lipid-based drug delivery systems for anti-cancer therapy.

SO CANCER DETECTION AND PREVENTION, (OCT 2002) Vol. 26, No. 4, pp. 299-307. Publisher: ELSEVIER SCI LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, OXON, ENGLAND.
ISSN: 0361-090X.

AU Koning G A (Reprint); Kamps J A A M; Scherphof G L

L8 ANSWER 2 OF 12 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
TI Pharmacokinetics of differently designed immunoliposome formulations in rats with or without hepatic colon cancer metastases.
AB Purpose: Compare pharmacokinetics of **tumor**-directed immunoliposomes in healthy and **tumor**-bearing rats (hepatic colon cancer metastases). Methods: A **tumor** cell-specific **monoclonal** antibody was attached to polyethyleneglycol-stabilized liposomes, either in a random orientation via a lipid anchor (MPB-PEG-liposomes) or uniformly oriented at the distal end of the PEG chains (Hz-PEG-liposomes). Pharmacokinetics and tissue distribution were determined using (3H)-cholesteryloleylether or bilayer-anchored 5-fluoro(3H)deoxyuridine-dipalmitate ((3H)FUdR-dP) as a marker. Results: In healthy animals clearance of PEG-(immuno)liposomes was almost log-linear and only slightly affected by antibody attachment; in **tumor**-bearing animals all liposomes displayed biphasic clearance. In normal and **tumor** animals blood elimination increased with increasing antibody density; particularly for the Hz-PEG-liposomes, and was accompanied by increased hepatic uptake, probably due to increased numbers of macrophages induced by **tumor** growth. The presence of antibodies on the liposomes enhanced **tumor** accumulation: uptake per gram **tumor** tissue (2-4% of dose) was similar to that of liver. Remarkably, this applied to **tumor**-specific and irrelevant antibody. Increased **immunoliposome** uptake by trypsin-treated

Kupffer cells implicated involvement of high-affinity Fc-receptors on activated macrophages. Conclusions: **Tumor** growth and **immunoliposome** characteristics (antibody density and orientation) determine **immunoliposome** pharmacokinetics. Although with a long-circulating **immunoliposome** formulation, efficiently retaining the prodrug FUdR-dP, we achieved enhanced uptake by hepatic metastases, this was probably not mediated by specific interaction with the **tumor** cells, but rather by **tumor**-associated macrophages.

SO Pharmaceutical Research (New York), (September, 2001) Vol. 18, No. 9, pp. 1291-1298. print.
ISSN: 0724-8741.

AU Koning, Gerben A.; Morselt, Henriette W. M.; Gorter, Arko; Allen, Theresa M.; Zalipsky, Samuel; Kamps, Jan A. A. M.; Scherphof, Gerrit L. (1)

L8 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 1

TI Study on third-type immunoliposomes loaded drugs and targeting in vitro and in vivo

AB The third-type **immunoliposome** (IML) loaded anticancer drugs-adriamycin (ADM) was prepd. from the conjugate of **monoclonal** antibody of human bladder cancer with PEG-COOH (**polyethylene glycol** carboxylic acid). The survival rate of the targeting EJ cells treated with IML-ADM (ADM = 45.45 .mu.g mL-) was 4.3.+-.1.0%, but 72% .+-. 6% for non-targeting LOVO cells in vitro. The **tumor** wt. in nude mice implanted by EJ cells was (39.+-.25), (135.+-.32), and (598.+-.240) mg by treatment with IML-ADM, SSL-ADM (steric stable liposomes carried Adriamycin), and normal saline for 27 d, resp. The results showed that the **immunoliposome**-mediated targeting anticancer drug was a feasible way.

SO Yaoxue Xuebao (2001), 36(7), 539-542
CODEN: YHHPAL; ISSN: 0513-4870

AU Hou, Xinpu; Zhang, Yufeng; Xie, Shusheng; Hu, Xin

L8 ANSWER 4 OF 12 SCISEARCH COPYRIGHT 2002 ISI (R)

TI Tumor targeting using anti-her2 immunoliposomes

AB We have generated anti-HER2 (ErbB2) immunoliposomes ILs), consisting of long circulating liposomes linked to anti-HER2 **monoclonal** antibody (MAb) fragments, to provide targeted drug delivery to HER2-overexpressing cells. Immunoliposomes were constructed using a modular strategy in which components were optimized for internalization and intracellular drug delivery. Parameters included choice of antibody construct, antibody density, antibody conjugation procedure, and choice of **liposome** construct. Anti-HER2 immunoliposomes bound efficiently to and internalized in HER2-overexpressing cells in vitro as determined by fluorescence microscopy, electron microscopy, and quantitative analysis of fluorescent probe delivery. Delivery via ILs in HER2-overexpressing cells yielded drug uptake that was up to 700-fold greater than with non-targeted sterically stabilized liposomes. In vivo, anti-HER2 ILs showed extremely long circulation as stable constructs in normal adult rats after a single i.v. dose, with pharmacokinetics that were indistinguishable from sterically stabilized liposomes. Repeat administrations revealed no increase in clearance, further confirming that ILs retain the long circulation and non-immunogenicity of sterically stabilized liposomes. In five different HER2-overexpressing xenograft models, anti-HER2 ILs loaded with doxorubicin (dox) showed potent anticancer activity, including **tumor** inhibition, regressions, and cures (pathologic complete responses). ILs were significantly superior vs. all other treatment conditions tested: free dox, liposomal dox, free MAb (trastuzumab), and combinations of dox + MAb or liposomal dox + MAb. For example, ILs produced significantly superior antitumor effects vs. non-targeted liposomes (P values from <0.0001 to 0.04 in eight separate experiments). In a non-HER2-overexpressing xenograft model (MCF7), ILs and non-targeted

liposomal dox produced equivalent antitumor effects. Detailed studies of **tumor** localization indicated a novel mechanism of drug delivery for anti-HER2 ILs. Immunotargeting did not increase **tumor** tissue levels of ILs vs. liposomes, as both achieved very high **tumor** localization (7.0-8.5% of injected dose/g tissue) in xenograft tumors. However, histologic studies using colloidal-gold labeled ILs demonstrated efficient intracellular delivery in **tumor** cells, while non-targeted liposomes accumulated within stroma, either extracellularly or within macrophages. In the MCF7 xenograft model lacking HER2-overexpression, no difference in **tumor** cell uptake was seen, with both ILs and non-targeted liposomes accumulating within stroma. Thus, anti-HER2 ILs, but not non-targeted liposomes, achieve intracellular drug delivery via receptor-mediated endocytosis, and this mechanism is associated with superior antitumor activity. Based on these results, anti-HER2 immunoliposomes have been developed toward clinical trials. Reenginecring of construct design for clinical use has been achieved, including: new anti-HER2 scFv F5 generated by screening of a phage antibody library for internalizing anti-HER2 phage antibodies; modifications of the scFv expression construct to support large scale production and clinical use; and development of methods for large-scale conjugation of antibody fragments with liposomes. We developed a scalable two-step protocol for linkage of scFv to preformed and drug-loaded liposomes. Our final, optimized anti-HER2 ILs-dox construct consists of F5 conjugated to derivatized PEG-PE linker and incorporated into commercially available liposomal doxorubicin (Doxil (R)).

Finally, further studies of the mechanism of action of anti-HER2 ILs-dox suggest that this strategy may provide optimal delivery of anthracycline-based chemotherapy to HER2-overexpressing cancer cells in the clinic, while circumventing the cardiotoxicity associated with trastuzumab + anthracycline. We conclude that anti-HER2 immunoliposomes represent a promising technology for tumor-targeted drug delivery, and that this strategy may also be applicable to other receptor targets and/or using other delivered agents.

SO JOURNAL OF CONTROLLED RELEASE, (6 JUL 2001) Vol. 74, No. 1-3, pp. 95-113. Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 0168-3659.

AU Park J W (Reprint); Kirpotin D B; Hong K; Shalaby R; Shao Y; Nielsen U B; Marks J D; Papahadjopoulos D; Benz C C

L8 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 2

TI Sterically stabilized anti-idiotype immunoliposomes improve the therapeutic efficacy of doxorubicin in a murine B-cell lymphoma model

AB A **liposome** contg. diverse synthetic lipid derivs. of **polyethylene glycol** (PEG) results in smaller distribution vol. and longer circulation time in blood and, thus, may improve drug targeting. The characteristics and therapeutic efficacy of immunoliposomes with similar liposomal formulation have never been studied in lymphoma models. The authors have developed immunoliposomes conjugated with S5A8 **monoclonal** antibody, an anti-idiotype antibody to 38C13 murine B-cell lymphoma, and loaded them with doxorubicin using an ammonium sulfate gradient. Purified antibodies were covalently coupled to the termini of PEG on the surface of small unilamellar liposomes. Cell binding and internalization ability of these immunoliposomes were estd. by a fluorescence assay using a pH-sensitive fluorescent dye (HPTS). The in vitro cytotoxicity of doxorubicin encapsulated in immunoliposomes was greater for idiotype-pos. 38C13 cells than for the idiotype-neg. variant of this cell line. In syngeneic C3H/HeN mice, doxorubicin encapsulated in immunoliposomes exhibited a long circulation time and was more effective at prolonging survival of mice bearing 38C13 **tumor** than non-targeted liposomal doxorubicin or free doxorubicin plus empty

immunoliposomes. The results demonstrate the superiority of targeted therapy with these immunoliposomes and its potential in lymphoma treatment.

SO International Journal of Cancer (1999), 80(5), 723-730
CODEN: IJCNAW; ISSN: 0020-7136

AU Tseng, Yun-Long; Hong, Ruey-Long; Tao, Mi-Hua; Chang, Fu-Hsiung

L8 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 3

TI In vivo targeting of surface-modified liposomes to metastatically growing colon carcinoma cells and sinusoidal endothelial cells in the rat liver

AB We prepd. immunoliposomes by covalent coupling of a randomly thiolated **monoclonal** antibody against the rat colon adenocarcinoma cell line CC531 to MPB-PE on the outer surface of conventional as well as PEGylated liposomes of about 100-nm diam. We attempted to target these immunoliposomes in vivo to CC531 cells growing metastatically in the liver of syngeneic rats. Only when the immunoliposomes contained PEG-DSPE, did we observe, both with fluorescent and radioactive labels, accumulation of label in many, but not all, metastatic nodules. The fluorescent label concd. in scattered areas within the nodules. By means of transmission electronmicroscopy, using colloidal gold particles as an encapsulated morphol. marker, we established that the large majority of the **tumor**-assocd. gold particles located in areas not contg. **tumor** cells. Most of the gold was detected in cells with a macrophage morphol. We tentatively ascribe this to either **tumor** morphol. or to the coupling procedure we applied for the prepn. of the immunoliposomes, or both. The random thiolation step of the antibody mol. conceivably allows for the exposure of the Fc portion of (part of) the antibody mols. so as to permit interaction with Fc receptors on the macrophages. Expts. with immunoliposomes prepd. either by coupling of the antibody specifically via its Fc portion or by using F(ab1)2 fragments are in progress. The crucial condition of liposomal longevity as in the above expts., where PEG-ylation of the immunoliposomes was necessary in order to achieve accumulation in the **tumor** area, by no means represents a general requirement for successful **liposome** targeting. We have shown that for efficient **liposome** targeting to a cell population which is readily accessible from the circulation, and has a high affinity for the liposomes, i.c. the hepatic sinusoidal endothelial cells, the presence of PEG chains may even be counter-productive.

SO Journal of Liposome Research (1997), 7(4), 419-432
CODEN: JLREE7; ISSN: 0898-2104

AU Scherphof, Gerrit L.; Kamps, Jan A. A. M.; Koning, Gerben A.

L8 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 4

TI Solid tumor treatment method using antitumor agent-containing liposomes with PEG coating and surface-attached antibody

AB A method of administering an antitumor compd. to a subject is disclosed. The method includes administering liposomes having sizes predominantly in the range 0.05 to 0.12 .mu., and contg. an antitumor compd. in **liposome**-entrapped form, a surface coating of **polyethylene glycol** chains, at a surface concn. thereof sufficient to extend the blood circulation time of the liposomes severalfold over that of liposomes in the absence of such coating, and surface-attached antibody mols. effective to bind specifically to **tumor**-assocd. antigens present at the **tumor** site. One **liposome** compn. includes doxorubicin in entrapped form, and, on the **liposome** surface, a **monoclonal** antibody against highly proliferating cells in a lung squamous cell carcinoma.

SO U.S., 17 pp., Cont.-in-part of U.S. 5,213,804.
CODEN: USXXAM

IN Allen, Theresa M.; Martin, Francis J.

L8 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 5

TI Targeting of stealth liposomes to erbB-2 (Her/2) receptor: In vitro and in vivo studies

AB Long-circulating (stealth) liposomes coated with **polyethylene glycol** (PEG), which show reduced uptake by the reticuloendothelial system (RES) and enhanced accumulation in tumors, were used for conjugation to **monoclonal** antibodies (MAbs) as a drug-targeting device. A MAb (N-12A5) directed against erbB-2 oncoprotein, a functional surface antigen, was used. Amplification and overexpression of the erbB-2 gene product, being unique to malignancy, confer onto this antibody-mediated therapy high **tumor** specificity. In vitro binding of [3H]cholesteryl ether ([3H]Chol ether) labeled anti-erbB-2 conjugated liposomes to N-87 cells (erbB-2-pos. human gastric carcinoma) was compared with the binding of non-targeted liposomes and indicated a 16-fold increase in binding for the targeted liposomes. No difference in binding to OV1063 cells (erbB-2-neg. human ovary carcinoma) was obsd. These results indicate highly selective binding of antibody-targeted liposomes to erbB-2-overexpressing cells. Despite increased cell binding, doxorubicin (DOX) loaded in anti-erbB-2-conjugated liposomes did not cause increased in vitro cytotoxicity against N-87 cells, suggesting lack of **liposome** internalization. In vivo, the crit. factor needed to decrease the non-specific RES uptake and prolong the circulation time of antibody-conjugated liposomes is a low protein to phospholipid ratio (<60 .mu.g .mu.mol-1). Using these optimized **liposome** prepns. loaded with DOX and by monitoring the drug levels and the [3H]Chol ether label, biodistribution studies in nude mice bearing s.c. implants of N-87 tumors were carried out. No significant differences in liver and spleen uptake between antibody-conjugated and plain liposomes were obsd. Nevertheless, there was no enhancement of **tumor liposome** levels over plain liposomes. Both **liposome** prepns. considerably enhanced DOX concn. in the **tumor** compared with free drug administration. Therapeutic expts. with N-87 **tumor**-bearing nude mice indicated that anti-**tumor** activity of targeted and non-targeted liposomes was similar, although both prepns. had an increased therapeutic efficacy compared with the free drug. These studies suggest that efficacy is dependent on drug delivery to the **tumor** and that the rate-limiting factor of **liposome** accumulation in tumors is the **liposome** extravasation process, irresp. of **liposome** affinity or targeting to **tumor** cells.

SO British Journal of Cancer (1996), 74(11), 1749-1756
CODEN: BJCAAI; ISSN: 0007-0920

AU Goren, D.; Horowitz, A. T.; Zalipsky, S.; Woodle, M. C.; Yarden, Y.; Gabizon, A.

L8 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 6

TI Development of immunoliposomes for targeting chemotherapy on cancer

AB A review, with 17 refs., mainly summarizing the authors' work on the development of **immunoliposome** for targeting chemotherapy on cancer. Human **monoclonal** antibodies, reactive to viable **tumor** cells, conjugated with antitumor drug (adriamycin)-intrapped liposomes were prepd. The **immunoliposome** was optimized by selection of dipalmitoyl-phosphatidylcholine and cholesterol as main lipid components, addn. of maleimidocaproyl-phosphatidylethanolamine for conjugation with the **monoclonal** antibodies, and surface modification with **polyethylene glycol**.

SO Aromatikkusu (1996), 48(5/6), 143-155
CODEN: AROMBO; ISSN: 0365-6187

AU Hosokawa, Saiko; Tagawa, Tosiaki; Hirakawa, Yoko; Nagaike, Kazuhiro

L8 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 7

TI Delivery of antisense oligodeoxyribonucleotides against the human epidermal growth factor receptor into cultured KB cells with liposomes conjugated to folate via **polyethylene glycol**

AB Antisense oligodeoxyribonucleotides targeted to the epidermal growth factor (EGF) receptor were encapsulated into liposomes linked to folate via a **polyethylene glycol** spacer (folate-PEG-liposomes) and efficiently delivered into cultured KB cells via folate receptor-mediated endocytosis. The oligonucleotides were a phosphodiester 15-mer antisense to the EGF receptor (EGFR) gene stop codon (AEGFR2), the same sequence with three phosphorothioate linkages at each terminus (AEGFR2S), a randomized 15-mer control of similar base compn. to AEGFR2 (RC15), a 14-mer control derived from a symmetrized Escherichia coli lac operator (LACM), and the 5'-fluorescein-labeled homologs of several of the above. Cellular uptake of AEGFR2 encapsulated in folate-PEG-liposomes was nine times higher than AEGFR2 encapsulated in nontargeted liposomes and 16 times higher than unencapsulated AEGFR2. Treatment of KB cells with AEGFR2 in folate-PEG-liposomes resulted in growth inhibition and significant morphol. changes. Curiously, AEGFR2 and AEGFR2S encapsulated in folate-PEG-liposomes exhibited virtually identical growth inhibitory effects, reducing KB cell proliferation by >90% 48 h after the cells were treated for 4 h with 3 .mu.M oligonucleotide. Free AEGFR2 caused almost no growth inhibition, whereas free AEGFR2S was only one-fifth as potent as the folate-PEG-**liposome**-encapsulated oligonucleotide. Growth inhibition of the oligonucleotide-treated cells was probably due to reduced EGFR expression because indirect immunofluorescence staining of the cells with a **monoclonal** antibody against the EGFR showed an almost quant. redn. of the EGFR in cells treated with folate-PEG-**liposome**-entrapped AEGFR2. These results suggest that antisense oligonucleotide encapsulation in folate-PEG-liposomes promise efficient and **tumor**-specific delivery and that phosphorothioate oligonucleotides appear to offer no major advantage over native phosphodiester DNA when delivered by this route.

SO Proceedings of the National Academy of Sciences of the United States of America (1995), 92(8), 3318-22
CODEN: PNASA6; ISSN: 0027-8424

AU Wang, Susan; Lee, Robert J.; Cauchon, Greg; Gorenstein, David G.; Low, Philip S.

L8 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 8

TI Liposomes for treatment of solid tumors

AB An anti-**tumor** compn. includes liposomes contg. an antitumor compd. in **liposome**-entrapped form, and with a surface coating of **polyethylene glycol** chains, at a surface concn. sufficient to extend the blood circulation time of the liposomes several-fold over that of liposomes in the absence of such coating. Attached to the free ends of a portion of the polymer chains are antibodies or antibody fragments effective to bind specifically to **tumor**-assocd. antigens present at the **tumor** site. One **liposome** compn. has sizes predominantly in the range 0.05-0.12 .mu.m, includes doxorubicin in entrapped form, and contains, on the PEG free ends, a **monoclonal** antibody specific against highly proliferative cells in a lung squamous cell carcinoma.

SO PCT Int. Appl., 49 pp.
CODEN: PIXXD2

IN Allen, Theresa M.; Martin, Francis J.; Woodle, Martin C.; Zalipsky, Samuel

L8 ANSWER 12 OF 12 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 9

TI Maleimidyl PEG derivative of phosphatidylethanolamine for preparation of functionalized pharmaceutical liposomes

AB A phosphatidylethanolamine deriv. comprising dimaleimidyl PEG attached (via a linker) to the ethanolamine moiety of phosphatidylethanolamine is described. This deriv. may be used to prep. liposomes with improved pharmacol. characteristics to which proteins, peptides, sugars, etc. may be attached. A thiol-modified phospholipid was prepd. by reaction of iminothiolane and dipalmitoylphosphatidylethanolamine. The thiol deriv.

was reacted with dimaleimidyl PEG and liposomes were prepd. using the product. A **monoclonal** antibody to a human **tumor** was conjugated to the resulting **liposome**. The antibody-**liposome** conjugate displayed affinity for the **tumor** cells.

SO Eur. Pat. Appl., 16 pp.
CODEN: EPXXDW

IN Tagawa, Toshiaki; Awane, Kaoru; Nagaike, Kazuhiro

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L8 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 4
AN 1996:449885 CAPLUS
DN 125:105097
TI Solid tumor treatment method using antitumor agent-containing liposomes with PEG coating and surface-attached antibody
IN Allen, Theresa M.; Martin, Francis J.
PA Sequus Pharmaceuticals, Inc., USA
SO U.S., 17 pp., Cont.-in-part of U.S. 5,213,804.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 9

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5527528	A	19960618	US 1993-40544	19930331
	US 5013556	A	19910507	US 1989-425224	19891020
	AU 9066374	A1	19910516	AU 1990-66374	19901019
	AU 642679	B2	19931028		
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	AU 9465272	A1	19941024	AU 1994-65272	19940330
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